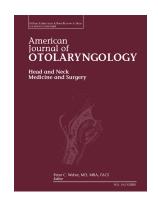


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Patterns and Clinical Outcomes of Olfactory and Gustatory Disorders in Six Months: Prospective Study of 1031 COVID-19 Patients

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Institution at which study was performed: Ain Shams University Pandemic Hospital at El-Obour city, Egypt

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Abstract

Objective: This study aims to comprehensively evaluate olfactory and gustatory dysfunctions during the COVID-19 pandemic regarding onset, course, associated symptoms, prognosis and relation to patients' demographics, treatment received and other symptoms.

Patients& Methods: This is a prospective study conducted on patients proven to be infected with COVID-19 and with olfactory/ guscatery dysfunction symptoms. Detailed history was taken from each patient about the onset of this dysfunction, associated symptoms. Then follow-up survey was done after 6 months to evaluate the prognosis.

Results: 1031 patients were included in the study, aged 18 to 69 years old, with 31.8 % were male. Olfactory/ gustatory dysfunctions occurred after other COVID-19 symptoms in 43.5% of cases, occurred suddenly in 80.4% and gradually in 19.6%. These dysfunctions were anosmia & ageusia in 50.2%, hyposmia & hypogeusia in 23.3%, anosmia alone in 17.7%, phantosmia in 18%, Parosmia in 28.4%. In terms of recovery 6-month follow up, 680 patients (66%) recovered completely, 22.1 % recovered partially while 11.9% did not recover. Most improvement occurred in the first two weeks. Headache, malaise, nasal obstruction and rhinorrhea were the commonest COVID-19 symptoms associated.

Conclusion: Most recovery of olfactory/ gustatory dysfunction in COVID-19 infection occurs at the first two weeks and is unrelated to patient demographics, treatment or olfactory training. Parosmia is an independent predictor for complete recovery, while phantosmia is significantly associated with lower probability of complete recovery.

Introduction

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) began and spread in China by the end of 2019 after that received worldwide attention. By the end of January 2020, WHO officially declared Coronavirus disease 2019 (COVID-19) epidemic as a public health energency of international concern and as a pandemic in March 2020. Since then, COVID-19 hits every corner of the world (1). Anosmia and taste disorders are considered main symptoms associated with the COVID-19 infection and as potential screening symptoms for suspecting and testing for COVID-12 (2,3). Nasal respiratory and olfactory cells express Angiotensin Converting Enzyme 2 proteins which are used by the COVID-19 virus to infect cells. Also, some strains of coronavirus could invade the olfactory bulb (4). Although olfactory and gustatory dysfunctions present as symptoms in 18 to 60% of COVID-19 patients and patients presenting with anosmia and influenzalike symptoms are 6-10 times more likely to be COVID-19 positive (5,6), there is no sufficient data in the literature regarding the course, recovery, associated

symptoms and prognosis of olfactory and gustatory symptoms. Our study aims to document all these missing data comprehensively using more than one thousand patient data.

Patients & Methods

This is a prospective study for olfactory and gustatory dysfunctions in COVID-19 patients evaluated at tertiary referral center and confirm ea to be positive by PCR of nasopharyngeal swab from 1st August 2020 to 31st Cotoper 2020. Inclusion criteria included patients with mild to moderate adult COVID-19 patients who presented with olfactory and/or gustatory dysfunctions. All patients with history of nasal or oral surgery or trauma, chronic chinosinusitis, previous history (before the pandemic) of olfactory or gustatory functions were excluded.

Detailed history was taken from each patient by physicians or nurses completing sheets to document the once of olfactory and gustatory dysfunction and associated symptoms. Then follow up survey was done after 6 months by phone call or physically to document the progression of olfactory and gustatory dysfunction and their prognosis. Data collection was conducted anonymously, and no reward was offered for completion.

The data involved demographics, smoking history, history of contact, medical comorbidities, associated COVID-19 symptoms. As regards olfactory and

gustatory dysfunctions, it included data about the presented form of dysfunction, time of onset, course, duration, time of recovery, treatment received, olfactory training usage, prognosis.

This study was approved by approved by Ain Shams University, Faculty of Medicine institutional review board. Patients were invited to participate. All patients signed informed written consent prior study started. All patients' data were dealt with complete confidentiality.

Statistical Methods

Data were analyzed using IBM© SPSC® Statistics version 26 (IBM® Corp., Armonk, NY). Categorical variables are presented as ratios or numbers and percentages and differences are compared using the Pearson chi-squared test or Fisher's exact test as appropriate. Ordinal data are compared using the chi-squared test for trends.

Multivariable binary logistic regression analysis is used to identify predictors of complete recovery. Predictors shown by bivariate analysis to be associated with the outcome at a level of $p \le 0.2$ were entered in multiple regression. We constructed the model using the enter method. P-values <0.05 are considered statistically significant.

Results

years old. Almost a third (32.4%) of these cases were in contact with confirmed COVID-19 cases. Abnormal smell presented in 97.9% of these cases while abnormal taste was in 75.7%. Anosmia presented in 67.9%, hyposmia in 30%, phantosmia in 18.0%, parosmia in 28.4%. In 43.5% of cases, smell/taste abnormalities occurred after COVID-19 symptoms Complete recovery of smell/taste changes occurred in 66% of cases, while partial recovery occurred in 22.1%. 70.1% of cases reached the best recovery in the first two weeks (Table 1).

After adjustment for the effect of coner factors, parosmia was an independent predictor for complete recovery (color ratio = 1.787, 95% CI = 1.304 to 2.449, p-value = 0.0003). On the other hand, phantosmia was significantly associated with lower probability of complete recovery (odds ratio = 0.281, 95% CI = 0.200 to 0.395, p-value < 0.0001). (Table 2,3,4, Figure 1,2,3)

Discussion

COVID-19 disease rapidly spreads across every corner world.

Otorhinolaryngologists may be in the front line due to the close contact with the

mucus membrane of the upper respiratory tract. Olfactory and gustatory dysfunctions are very characteristic symptoms of the disease. So, this study is primarily concerned with olfactory and gustatory dysfunctions during the pandemic, comprehensively evaluating the onset, course and relation to the COVID-19 course and its symptoms. This study was done in a pandemic hospital on confirmed COVID-19 adult patients by PCR, who had symptoms of olfactory and gustatory dysfunctions. 1031 patients were included in our study, aged 18 to 69 years old, with 31.8 % were male. 86.8 % were non-smokers, 89.9% had no comorbidities. 32.4% of these cases were in contact with confirmed COVID-19 cases, and 76.7% sought prior medical advice.

In their study on 268 patients, Oscolo-Rizzo et al reported interquartile range of age was 38–56 years with female preponderance 61.9%, co morbidities were reported in 34.0% (7). Hepkins et al did their study on 382 patients, age ranged between 18-79 years old. 74.6% were female (4). Lechien et al did their study on 1363 patients aged 41.9 ± 13.0 years old, 62.9% were female, 11.4% were smokers (8).

In our study, baseline sociodemographic and lifestyle factors were not associated with olfactory/ taste dysfunction persistence. This agrees with Oscolo-Rizzo et al (7).

In our study, olfactory/ gustatory dysfunctions occurred before other COVID-19 symptoms in 19.4% of cases, with other COVID-19 symptoms in 37.1% and after in 43.5%. Olfactory/ gustatory dysfunctions occurred suddenly in 80.4% and gradually in 19.6%. These dysfunctions were anosmia & ageusia in 518 patients (50.2%), hyposmia & hypogeusia in 240 (23.3%), anosmia alone in 17.7%, hyposmia alone in 6.7%, hypogeusia alone in 1.1%, ageusia alone in 1.1%. Phantosmia occurred in 186 cases (18%), 16.1% of them recovered. Parosmia occurred in 28.4%, of which 24.3% recovered.

According to Lechien et al, anosmia formed 81.6% of the cases while hyposmia formed 18.4%. Dysgeusia was 55.9%. Phantosmia formed 16.4%. Olfactory dysfunction developed after other COVID-19 symptoms in 44.7%, before in 16.8% (8). In their study, Hopkins et al found 86.4% with anosmia and 11.5% with hyposmia. 14.9% reported smell changes before the onset of other COVID-19 symptoms, 39.3% at the same time and 45.8% after (4).

According to Oscolo-Rizzo et al, 81.3% reported combined olfactory/ taste dysfunctions, 10.2% reported isolated smell impairment, 8.6% reported isolated taste disorder (7).

In terms of recovery of olfactory/ gustatory dysfunctions after 6-month follow up, 680 patients (66%) recovered completely, 22.1 % recovered partially while 11.9%

did not recover. Most improvement occurred in the first two weeks (in 637 /908 patients (70.1%)). This agrees with Hopkins et al who stated a significant recovery rate in the first 2 weeks but then it became plateau (4).

Oscolo-Rizzo et al reported 69.5% complete recovery after 12 months, 21.9% partial recovery and 8.6% no improvement (7). Hopkins et al stated improvement rate was 79% while 17.3% had persistent anosmia after 4 weeks of follow up (4).

According to Lechien et al, over one third of the rations recovered from olfactory dysfunction in the first two weeks, 54.3% recovered after one month. 24.5% did not recove after two months. Recovery rate ranges from 75% to 85% in the first two months (8)

In terms of other COVID-19 symptoms in patients in the current study, headache occurred in 48.7%, malaise in 49%, rhinorrhea / nasal obstruction in 30.6%, fever in 26.9%, cough in 32.6% sore throat in 26.4%. According to Lechien et al, the most common associated COVID-19 symptoms were asthenia 86.3%, headache 69.9% and rhinorrhea 64.4%, nasal obstruction 62.1% (8)

In our study, 30.3% received intranasal steroids, 6% received systemic steroids, 10.1% received Omega-3 fatty acids while 20.1% did not receive any treatment. 55.2 % of patients were not aware of olfactory training, 18.9% were aware, but didn't not practice it. 10% were aware but practiced it inappropriately. 15.9% were

aware and practiced it appropriately. But there was no statistically significant association between using olfactory training and recovery. This agrees with Hopkins et al (4).

In their study on 30 patients with olfactory and gustatory dysfunction, Konstantinidis et al found smell and taste changes in 70%, only smell changes in 26.6%, only taste changes in 3.3%. 63.3% recovered completely, 36.6% with partial or no recovery after 4 weeks of follow up. Nasal obstruction was reported in 16.6%, rhinorrhea in 10%, parosmia and phantosmia in 13%, dysgeusia in 10% (9). Renaud et al concluded a 96.1% recovery rate from COVID-19 olfactory dysfunction after 1 year of follow up. (1))

Olfactory dysfunction may have different course and progression in COVID-19 patients. According to studie: this is due to differences in the expression of ACE2 between individuals. The nore expression of these proteins is mostly associated with longer duration of smell changes and more injury to stem neuron cells in the olfactory bulb. (11,12)

By analyzing every factor in the current study in terms of improvement of olfactory/ gustatory dysfunctions or complete recovery after adjustment for the effect of other factors, we found a statistically significant association between parosmia and partial or complete recovery. Also, parosmia was an independent

predictor for complete recovery while phantosmia was significantly associated with lower probability of complete recovery.

Conclusion

Most recovery of olfactory/ gustatory dysfunction in COVID-19 infection occurs at the first two weeks and is unrelated to patient demographics, treatment or olfactory training. Parosmia is an independent predictor for complete recovery while phantosmia is significantly associated with lower probability of complete recovery.

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Tables

Table 1. Characteristics of the study population

Variable	Count	Valid percentage
Age category (years)		
18-20	45	4.4%
21-30	524	50.9%
31-40	344	33.4%
41-50	97	9.4%
51-60	17	1.7%
61-70	3	0.3%
<u>Sex</u>		
M	328	31.8%
F	703	68.2%
Past history		
Smoking	136	13.2%
Medical comorbidities	104	10.1%
Contact with confirmed COVID-19 cr.s.	334	32.4%
Sought prior medical advice	791	76.7%
General manifestations of CO VT -19		
Dry cough	178	17.3%
Product cough	158	15.3%
Dyspnea	194	18.8%
Rhinorrhea / Nasal obstruction	316	30.6%
Malaise	505	49.0%
Diarrhea	250	24.2%
Nausea	170	16.5%
Fever	277	26.9%

Sore throat	272	26.4%
Headache	502	48.7%
Abdominal pain	241	23.4%
Presentation of the smell / taste disorder		
Hyposmia only	69	6.7%
Hypogeusia only	11	1.1%
Hyposmia & Hypogeusia	240	23.3%
Anosmia only	182	17.7%
Ageusia only	11	1.1%
Anosmia & Ageusia	518	50.2%
Occurrence of complex forms of smell diorders		
Phantosmia		
Did not occur	845	82.0%
Occurred transiently then recovered	166	16.1%
Occurred and did not recover	20	1.9%
Parosmia		
Did not occur	738	71.6%
Occurred transiently then a rowered	251	24.3%
Occurred and did not recover	42	4.1%
Overall prevalence of individual forms of smell / taste abnormality		
Hyposmia	309	30.0%
Hypogeusia	251	24.3%
Anosmia	700	67.9%
Ageusia	529	51.3%
Abnormal smell (hyposmia or anosmia)	1009	97.9%

Abnormal taste (hypogeusia or ageusia)	780	75.7%
Phantosmia	186	18.0%
Parosmia	293	28.4%
Onset of smell/ taste changes		
Gradual	202	19.6%
Sudden	829	80.4%
Onset of smell / taste changes in relation to COVID-19 symptoms		
Before COVID-19 symptoms	200	19.4%
During COVID-19 symptoms	383	37.1%
After COVID-19 symptoms	448	43.5%
Treatment received for smell / taste changes		
Intranasal steroids	312	30.3%
Systemic steroids	62	6.0%
Omega-3 FA	104	10.1%
Others	305	29.6%
Combination of medications	41	4.0%
Nil	207	20.1%
Awareness of patient about smell training		
Not aware about it	569	55.2%
Aware, does not practice it	195	18.9%
Aware, practices it inappropriately	103	10.0%
Aware, practices it appropriately	164	15.9%
Recovery of smell / taste		
Not recovered	123	11.9%
Recovered partially	228	22.1%

0/908	34.1%
'/908	26.001
	36.0%
1/908	11.5%
908	6.9%
908	2.3%
908	4.5%
908	4.6%
44.	7908 7908 7908 7908 7908

Table 2. Predictors of improvement

	No re	covery	Partial or	complete	
	(n=	=123)	recovery (n=908)		
Variable	N	%	N	%	p-value
Age category (years)					0.449†
10-20	4	3.3%	41	4.5%	
21-30	68	55.3%	456	50.3%	
31-40	41	33.3%	303	33.4%	
41-50	7	5.7%	90	9.9%	
51-60	3	2.4%	14	1.5%	
61-70	0	0.0%	3	0.3%	
Sex					0.700‡
M	41	33.3%	287	31.6%	
F	82	66.7%	621	68.4%	

Past history					
Smoking	19	15.4%	117	12.9%	0.431‡
Medical comorbidities	14	11.4%	90	9.9%	0.611‡
Contact with confirmed COVID-19 case	41	33.3%	293	32.3%	0.813‡
Sought prior medical advice	93	75.6%	698	76.9%	0.756‡
General manifestations of COVID-19					
Dry cough	15	12.2%	163	18.0%	0.113‡
Product cough	16	13.0%	742	15.6%	0.447‡
Dyspnea	21	17.1%	173	19.1%	0.598‡
Rhinorrhea / Nasal obstruction	32	2(3.07)	284	31.3%	0.235‡
Malaise	54	+3.9%	451	49.7%	0.230‡
Diarrhea	25	20.3%	225	24.8%	0.279‡
Nausea	15	12.2%	155	17.1%	0.171‡
Fever	25	20.3%	252	27.8%	0.081‡
Sore throat	34	27.6%	238	26.2%	0.735‡
Headache	56	45.5%	446	49.1%	0.455‡
Abdominal pain	24	19.5%	217	23.9%	0.281‡
Presentation of the smeh 'taste disorder					0.268§
Hyposmia only	6	4.9%	63	6.9%	
Hypogeusia only	2	1.6%	9	1.0%	
Hyposmia & Hypogeusia	28	22.8%	212	23.3%	
Anosmia only	30	24.4%	152	16.7%	
Ageusia only	0	0.0%	11	1.2%	
Anosmia & Ageusia	57	46.3%	461	50.8%	
Overall prevalence of individual forms of					

smell / taste abnormality					
Hyposmia	34	27.6%	275	30.3%	0.548‡
Hypogeusia	30	24.4%	221	24.3%	0.990‡
Anosmia	87	70.7%	613	67.5%	0.473‡
Ageusia	57	46.3%	472	52.0%	0.240‡
Abnormal smell	121	98.4%	888	97.8%	1.000§
Abnormal taste	87	70.7%	693	76.3%	0.175‡
Phantosmia	20	16.3%	766	18.3%	0.584‡
Parosmia	0	0.0%	293	32.3%	<0.001;
Onset of smell/ taste changes					0.483‡
Gradual	27	_2.0%	175	19.3%	
Sudden	26	78.0%	733	80.7%	
Onset of smell / taste changes in relation	to				0.941†
COVID-19 symptoms					
Before COVID-19 symptoms	23	18.7%	177	19.5%	
During COVID-19 symptoms	48	39.0%	335	36.9%	
After COVID-19 symptoms	52	42.3%	396	43.6%	
Treatment received for s. ren / taste					
<u>changes</u>					
Intranasal steroids	39	31.7%	273	30.1%	0.710‡
Systemic steroids	4	3.3%	58	6.4%	0.170‡
Omega-3 FA	13	10.6%	91	10.0%	0.850‡
Others	36	29.3%	269	29.6%	0.935‡
Combination of medications	4	3.3%	37	4.1%	0.809§
Nil	27	22.0%	180	19.8%	0.580‡

Smell training					0.578†
Not aware about it	76	61.8%	493	54.3%	
Aware, does not practice it	15	12.2%	180	19.8%	
Aware, practices it inappropriately	11	8.9%	92	10.1%	
Aware, practices it appropriately	21	17.1%	143	15.7%	

Data are number (N) and percentage (%).

- †. Pearson chi-squared test.
- ‡. Fisher's exact test.
- §. Chi-squared test for trend.

Table 3. Predictors of complete recovery

	No or	partial	Complet		
	recovery	y (n=351)	(n=		
Variable	N	%	N	%	p-value
Age category (years)					0.966†
10-20	13	3.70%	32	4.70%	
21-30	182	51.90%	342	50.40%	
31-40	118	33.60%	226	33.30%	
41-50	30	8.50%	67	9.90%	
51-60	7	2.00%	10	1.50%	
61-70	1	0.30%	2	0.30%	
<u>Sex</u>					0.173‡
M	102	29.10%	226	33.20%	
F	249	70.90%	454	66.80%	

Past history					
Smoking	47	13.40%	89	13.10%	0.892‡
Medical comorbidities	37	10.50%	67	9.90%	0.728‡
Contact with confirmed COVID-19 case	120	34.20%	214	31.50%	0.377‡
Sought prior medical advice	260	74.10%	531	78.10%	0.148‡
General manifestations of COVID-19					
Dry cough	60	17.10%	118	17.40%	0.917‡
Product cough	56	16.00%	102	15.00%	0.687‡
Dyspnea	69	19. 70%	125	18.40%	0.619‡
Rhinorrhea / Nasal obstruction	110	s1.30%	206	30.30%	0.730‡
Malaise	170	40.40%	335	49.30%	0.800‡
Diarrhea	16	21.70%	174	25.60%	0.162‡
Nausea	53	15.10%	117	17.20%	0.388‡
Fever	95	27.10%	182	26.80%	0.918‡
Sore throat	91	25.90%	181	26.60%	0.811‡
Headache	165	47.00%	337	49.60%	0.438‡
Abdominal pain	80	22.80%	161	23.70%	0.751‡
Presentation of the smeh ' taste disorder					0.178§
Hyposmia only	18	5.10%	51	7.50%	
Hypogeusia only	5	1.40%	6	0.90%	
Hyposmia & Hypogeusia	87	24.80%	153	22.50%	
Anosmia only	73	20.80%	109	16.00%	
Ageusia only	4	1.10%	7	1.00%	
Anosmia & Ageusia	164	46.70%	354	52.10%	
Overall prevalence of individual forms of					

smell / taste abnormality					
Hyposmia	105	29.90%	204	30.00%	0.977‡
Hypogeusia	92	26.20%	159	23.40%	0.316‡
Anosmia	237	67.50%	463	68.10%	0.853‡
Ageusia	168	47.90%	361	53.10%	0.112‡
Abnormal smell	342	97.40%	667	98.10%	0.492‡
Abnormal taste	260	74.10%	520	76.50%	0.396‡
Phantosmia	104	29.60%	82	12.10%	<0.001‡
Parosmia	84	23. 00%	209	30.70%	0.022‡
Onset of smell / taste changes					0.839‡
Gradual	70	1>.90%	132	19.40%	
Sudden	2 1	80.10%	548	80.60%	
Onset of smell / taste changes in relation					0.628†
to COVID-19 symptoms					
Before COVID-19 symptoms	66	18.80%	134	19.70%	
During COVID-19 symptoms	129	36.80%	254	37.40%	
After COVID-19 symptoms	156	44.40%	292	42.90%	
Treatment received for sinen/ taste					
<u>changes</u>					
Intranasal steroids	112	31.90%	200	29.40%	0.408‡
Systemic steroids	19	5.40%	43	6.30%	0.560‡
Omega-3 FA	36	10.30%	68	10.00%	0.897‡
Others	107	30.50%	198	29.10%	0.649‡
Combination of medications	12	3.40%	29	4.30%	0.510‡
Nil	65	18.50%	142	20.90%	0.369‡

Patient awareness of smell training					0.145†
Not aware about it	207	59.00%	362	53.20%	
Aware, does not practice it	62	17.70%	133	19.60%	
Aware, practices it inappropriately	29	8.30%	74	10.90%	
Aware, practices it appropriately	53	15.10%	111	16.30%	

Data are number (N) and percentage (%).

- †. Pearson chi-squared test.
- ‡. Fisher's exact test.
- §. Chi-squared test for trend.

Table 4. Multivariable binary logistic regression for prodictors of complete recovery

Variable	В	, E ,	Wald	p-value	Odds ratio	95% CI
Female sex (=1)	-0.25.	3.148	2.485	0.115	0.792	0.592 to 1.059
Seeking prior medical advice (=1)	073	0.159	1.190	0.275	1.189	0.871 to 1.624
Diarrhea (=1)	0.252	0.162	2.435	0.119	1.287	0.938 to 1.767
Ageusia (=1)	0.240	0.136	3.088	0.079	1.271	0.973 to 1.661
Phantosmia (=1)	-1.271	0.174	53.303	<0.0001	0.281	0.200 to 0.395
Parosmia (=1)	0.580	0.161	13.029	0.0003	1.787	1.304 to 2.449
Constant	0.604	0.195	9.586	0.002		

B= regression coefficient, SE= standard error, Wald= Wald statistics, 95% CI= 95% confidence interval for odds ratio.

Figure Legends

- Figure 1. Prevalence of parosmia among patients experiencing partial or complete recovery versus those experiencing no recovery.
- Figure 2. Prevalence of phantosmia among patients experiencing complete recovery versus those experiencing no or partial recovery.
- Figure 3. Prevalence of parosmia among patients experiencing complete recovery versus those experiencing no or partial recovery.